REMARKS

I. Introduction

Dr. Helms and Dr. Tungaturthi are thanked for the courtesies extended Applicants and their counsel during an interview regarding this application on October 20, 2005.

Applicants respectfully request reconsideration of the present application for the following reasons. Claims 1-5, 7-16, 20-23, 30, 33, 37, 40-41 and 44-45 are pending and presented for reconsideration.

II. Response to Issues Raised by Examiner in Outstanding Office Action

a. Claim Rejections - 35 U.S.C. § 103

Claims 1-16, 20-23, 30, 33, 35-43, and 44-45 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Bohlen et al (Blood 82: 1803-1812, 1993) ("Bohlen") and further in view of Mack et al (PNAS 92: 7021-7025, 1995) ("Mack") and as evidenced from the specification and Blattler et al. (US Patent 5,239,062) ("Blattler"). Office Action dated 08/03/05, p. 3. Applicants respectfully request reconsideration and withdrawal of the rejection. Applicants submit the declaration of Dr. Baeuerle and Dr. Kufer ("the Declaration") in support of the nonobviousness arguments presented below.

The Examiner asserts that Bohlen teaches a bispecific molecule directed to the CD19 and CD3 antigens. Office Action, dated 08/03/05, p. 3. However, the Examiner concedes that Bohlen does not teach a single-chain bispecific CD19 x CD3 antibody. Id. The Examiner contends that the teachings of Mack and Blattler remedy these deficiencies. The Examiner cites Mack as disclosing a bispecific single chain antibody that binds CD3 and 17-1 in the claimed orientation. Id. The Examiner has applied Blattler, in the past, as teaching that the CD19 antigen is expressed in all B-CLL and all non Hodgkin's lymphomas. Office Action, dated 01/20/04, p. 9.

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time that the invention was made to produce a single-chain bispecific antibody from the bispecific antibody of Bohlen by the method of Mack for the

treatment of non-Hodgkin's lymphoma. Id. The Examiner further alleges that one skilled in the art would have been motivated, and had a reasonable expectation of success to produce a single-chain bispecific antibody as set forth above because Bohlen teaches that a bispecific binding agent which binds CD19 and human CD3 can be used for the treatment of B-CLL, and as taught by Blattler, the CD19 antigen is expressed in all B cell non-Hodgkin's lymphomas. Id., p. 9-10. Therefore, the Examiner further alleges that it would have been obvious to treat Non-Hodgkin's lymphoma with a bispecific molecule, a bispecific antibody directed to CD19 and CD3. Id., p. 10.

To establish a *prima facie* case of obviousness, however, there needs to be (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) the prior art references, when combined, must teach or suggest all the limitations of the claimed invention. *See* MPEP §2143. "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "It is difficult but necessary that the decision maker forget what he or she has been taught ...about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Applicants respectfully assert that the examiner has not met his burden.

In addition MPEP § 2143.01 provides:

> II. WHERE THE TEACHINGS OF THE PRIOR ART CONFLICT, THE EXAMINER MUST WEIGH THE SUGGESTIVE POWER OF EACH REFERENCE
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> The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one

reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991).

i. Bohlen, Blattler, and Mack

As the Examiner concedes, Bohlen does not disclose the use of a single-chain bispecific CD19 x CD3 antibody. Office Action, p. 3. Applicants assert that Bohlen in fact teaches away from the present claimed invention because Bohlen additionally requires the use of an anti-CD28 co-stimulatory antibody to achieve its cytotoxicity (see abstract and Table 3 of Bohlen). The presently claimed invention does not require any co-stimulatory agents and in fact teaches on page 4, first full paragraph of the specification that no co-stimulatory agents are necessary. MPEP §2144.04 II (B) states that the omission of an element and retention of its function is an indicia of unobviousness, citing *In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966). This is clearly the case for the presently claimed invention.

In addition, Bohlen does not describe methods for the treatment of non-Hodgkin's lymphoma with an antibody. (See the Declaration, section 2) The Examiner attempts to remedy these deficiencies by relying on Mack and Blattler. However, a person of skill in the art at the time the invention was made, reading Mack and Blattler, would not have been motivated to combine the teaching of these references with Bohlen, nor would there have been any reasonable expectation of success in doing so.

A person of skill in the art at the time the invention was made, reading Mack, would not have been motivated to modify Bohlen's bispecific antibody through use of Mack's bispecific single-chain antibody. The potency of Mack's 17-1A x CD3 bispecific antibody in redirected lysis of various tumor cells is **very low** and is not different from the potency of monoclonal antibodies described in the literature (See Mack Figures 5 and 6 on page 7024 and section 2 of the Declaration). Half maximal target cell lysis is observed at concentrations of 17-1A x CD3 bispecific antibody between 1.6 and 40 ng/ml. This low level of activity is achieved by whole antibodies as well, and is not attractive. This lack of activity is particularly unattractive given the low productivity of the 17-1A x CD3 bispecific antibody of only 12-15 mg/L in CHO cells (see page 7023).

It would have been readily apparent to the skilled artisan at the time the invention was made that Mack's bispecific antibody was not suited for clinical use because of the

excessive costs associated with production and treatment. To be an attractive candidate, the productivity of the 17-1A x CD3 bispecific antibody required dramatic improvement, or the 17-1A x CD3 bispecific antibody had to be more efficacious by at least 100 fold. (See section 2 of the Declaration)

On page 7025 of the Mack article, the use of a 17-1A x CD3 bispecific antibody for the treatment of minimal residual disease is proposed. In contrast, the claimed invention of the present application may be used in late-stage lymphoma, such as non-Hodgkin lymphoma (NHL). In NHL, massive amounts of tumor cells, sometimes in the kg-range, must be eliminated by a bispecific antibody. These tumor cells can float freely in peripheral blood or lymph nodes, but can also manifest as very large tumors. A bispecific antibody that can remove large tumor masses as found with certain blood-borne cancers is not described by Mack.

An antibody for the treatment of NHL must have a different specificity than the 17-1A x CD3 bispecific antibody because lymphoma cells are devoid of 17-1A antigen. The selection of an appropriate target antigen to address lymphoma is a challenging task. At the time the invention was made, CD19 would not have been an attractive candidate because it was known to rapidly internalize upon binding by monoclonal antibodies. See discussion above. Internalization of CD19 in the case of bispecific antibodies would prevent recruitment of T cells and redirected lysis of tumor cells.

Likewise, Blatter fails to provide the motivation to remedy the deficiencies of the Bohlen and Mack references. In section 2 of their Declaration, Dr. Baeuerle and Dr. Kufer conclude that Blattler teaches away from use of an antibody to CD19 as a therapeutic. Blattler teaches use of antibodies in combination with a toxic molecule. The toxic molecule is transported into the cell following antigen binding. (See, for example, column 19, lines 20-51 and column 5, lines 23-52) Dr. Baeuerle and Dr. Kufer conclude in section 2 of their Declaration that since the claimed invention of the instant application must not be internalized in order to effectively function as an anti-cancer agent recruiting cancer cells, a person of ordinary skill in the art at the time the invention was made would not believe that a single-chain construct utilizing CD19 would have a reasonable expectation of success in the desired cancer treatment regimen.

Following analysis of the prior art, including a careful analysis of the teachings of Bohlen, Blattler, and Mack, a person of ordinary skill in the art at the time the invention was made would not have been motivated to modify Bohlen, based on the teachings of Mack and Blattler, to make the claimed invention. The Examiner has failed to present a *prima facie* case of obviousness and it is respectfully requested that the rejection be withdrawn.

ii. Kipriyanov 1997 Teaches Away from the Claimed Invention

In order to expedite prosecution, and without prejudice to pursuing original claim 1 in a continuing application, Applicants have amended independent claims 1, 21, and 30 to include the limitation of a single chain multi-functional peptide arranged in the order V_LCD19-V_HCD19-V_HCD3-V_LCD3. Nevertheless, Applicants reassert arguments made in the previously filed Amendments of July 20, 2004 and March 28, 2005.

Applicants believe that an analysis of the prior art at the time of filing would not lead a person of ordinary skill in the art to this claimed invention. In **1997**, before the earliest priority date of the instant application, Kipriyanov presented findings at an international conference on the use of a CD3 x CD19 antibody in the lysis of malignant human B-cells. The conference was sponsored by important companies such as Biomira and Antisoma, among others. See Kipriyanov et al, Abstract for the Fourteenth International Conference on Advances in the Application of Monoclonal Antibodies in Clinical Oncology, Greece, May 1997 ("Kipriyanov 1997"). Kipriyanov 1997 reports pursuing two avenues of research including the creation of single chain antibodies. The Kipriyanov 1997 publication explicitly states that:

> For the creation of a bispecific anti human CD3-CD19 antibodies, two different strategies were utilized. A single chain $(scFv)_2$ antibody, where the individual scFv regions were joined by a 20 amino acid linker, and a non-covalent heterodiner were constructed. **The soluble diabody proved to be produced by *E. coli* at a much higher yield than $(scFv)_2$,** consisted of only dimers after IMAC purification and specifically interacted with both CD3 and CD19 positive cells. **The $(scFv)_2$ construct, however, failed to recognize human CD3. . . . The diabody is potent in retargeting peripheral blood lymphocytes to lyse tumour cells expressing the CD19 antigen.** (Emphasis added)

This Abstract was presented at an important international scientific conference in May 1997 and provides evidence to one skilled in the art that a single chain bispecific antibody of CD3 x CD19 had been produced, tested, and shown to have no binding to human CD3. Kipriyanov 1997 not only teaches away from a single chain bispecifc antibody of CD3 x CD19, but directs the reader to an alternative approach, a "non-covalent heterodimer diabody" that is taught to be "potent in retargeting peripheral blood lymphocytes to lyse tumour cells expressing the CD19 antigen."[1] Kipriyanov is a very clear teaching away from the claimed invention, published before the earliest priority date of the instant application.

Kipriyanov 1997 attempted to take advantage of a bispecific CD3 x CD19 single chain antibody and found the antibody failed to recognize human CD3. Following the experiments of Kipriyanov 1997, a person of ordinary skill in the art would conclude that a bispecific single chain construct of CD3 and CD19 had been tested and could not properly function. There could be no reasonable expectation of success in pursuing such research because bispecific single chain antibodies had been produced and shown to lack CD3 binding, an element of the claimed invention.

Applicants believe that Kipriyanov 1997 provides results that must be considered during any analysis of whether the claims are obvious in view of the prior art. See MPEP § 2143.01. It is well settled law that prior art **teaching away** from the claimed invention is highly relevant in any determination of whether the claimed invention would have been obvious. See, for example, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Since Kipriyanov 1997 teaches away from a single-chain bispecific CD3-CD19 antibody, the claimed invention cannot be found obvious in view of Bohlen, Mack and Blattler.

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[1] In order to aid the Examiner in the analysis of claimed single-chain bispecific antibodies, and those found in the prior art, Dr. Baeuerle and Dr. Kufer provide a chart in their Declaration. At the top of the chart is a description of the antibodies claimed in the instant invention. The second antibody is that taught by Mack. The third antibody is the non-covalent heterodimer diabody taught by Kipriyanov 1997.

iii. Superior Results

Despite the above reasoning, which Applicants believe is more than sufficient to overcome the obviousness rejection, Applicants have provided additional data in the Declaration demonstrating that the claimed invention shows far superior results when compared to other constructs. As provided in MPEP § 716.02(a), greater than expected results are evidence of nonobviousness. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985)

The experiments provided in the Declaration directly compare bispecific single-chain antibodies having the domain arrangement V_LCD19-V_HCD19-V_HCD3-V_LCD3 with a well characterized covalent heterodimer diabody called Tandab.[2] Previous studies showed by direct side-by-side comparison that Tandab (called LL-Tandab in the citation below) was more active than non-covalent heterodimer diabodies. (Kipriyanov et al, (1999), *J Mol Biol* **293**, 41-56). For example, Kipriyanov 1999 states on page 51 that "[t]he Tandabs were consistently more effective than the diabody for inducing T cell proliferation in the presence of tumor cells and in effector cell retargeting." Tandab is one of the best documented and studied heterodimer diabodies in this area of study. Tandab is therefore a well documented benchmark by which to compare the claimed invention with other similar constructs. See the Declaration at section 4. The amino acid sequence of Tandab is provided in Figure 1 of the Declaration.

The claimed antibodies were consistently more active than Tandab and, depending on target cell line and pre-treatment of T cells had ED_{50} values between two and four orders of magnitude improved over Tandab. (See Sections 3-7, Figures 4-5 and Table 1 of the Declaration). Multiple V_LCD19-V_HCD19-V_HCD3-V_LCD3 antibodies were characterized and found to all have similar assay activity. (See Section 6 and Figures 6 and 7 of the Declaration). These findings underscore the remarkable and unexpected efficacy of the

[2] We refer the Examiner to the fourth antibody molecule, or Tandab, described in the chart found in the Declaration

claimed invention in comparison to other modes of antibody treatment. (See Declaration Sections 4-7).

Applicants believe that these studies provide additional evidence of nonobviousness. A difference of two to four orders of magnitude over the Tandab antibody, identified in the scientific literature as the best CD3 x CD19 antibody is remarkable and significant. Such a finding is ample evidence of superior results and a sufficient basis for overcoming the Examiner's rejection.

For all of the above reasons, including the lack of a *prima facie* case of obviousness based on the Bohlen, Mack and Blattler references, the clear teaching away from the claimed invention in Kipriyanov 1997, and the unexpected superiority of the claimed antibodies when compared to those in the prior art, the Examiner is respectfully requested to withdraw the obviousness rejection and allow the presently pending claims.

b. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 11 and 44-45 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph for lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts, "although the claims require binding as stated in the response, the specification as well as the prior art does not teach an antibody with only one CDR that binds. Therefore, one skilled in the art would not expect antibodies as claimed which do not have a full set of CDRs to bind antigen." Office Action, dated 08/03/2005, p. 3.

Applicants submit that claim 45 includes domains with three CDRs and is, therefore, conceded by the Examiner to be enabled. In addition, claim 44 relates to antibodies with two CDRs. Applicants previously submitted references by Olsen and Rudikoff regarding modification of antibody CDR regions. Olsen found that one of the CDRs was dispensable. This study provides direct evidence for antibody binding with two CDRs, as provided in claim 44.

For claim 11, the Examiner asserts that a person of skill in the art would "not expect the antibodies as claimed ... to bind antigen." Id. It is well settled that "[a]ny analysis of

whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." MPEP, 8th ed. Rev.2, 2164.01. See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). A person of skill in the art would be able to make and use CD19 x CD3 single chain constructs with fewer than a full compliment of CDRs and test their specific binding using methods within the specification. Such tests would indicate whether the new antibody still showed specific binding and would, therefore, fall within the scope of the claims.

Applicants refer the Examiner to the arguments in the 03/28/05 Office Action Response providing extensive arguments as to why the claimed invention is consistent with an analysis of the Wands factors. In light of these arguments, Applicant's respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

It is acknowledged that these Remarks and the Declaration are submitted after final rejection. However, because the Remarks and Declaration do not introduce new matter, but place the application in condition for allowance, or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

Applicants believe the application is in condition for allowance. However, in order to maintain pendency of the application, Applicants are filing a Notice of Appeal.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date October 28, 2005 By Richard Peet

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5483
Facsimile: (202) 672-5399

Richard Peet
Attorney for Applicant
Registration 35,792